Induction Chemoradiotherapy Increases Pleural and Pericardial Complications after Esophagectomy for Cancer

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Hypothesis: Limited information is available on late complications of multimodality therapy for locally advanced esophageal cancer. This study focuses on postesophagectomy benign pleural and pericardial complications to determine their prevalence, temporal pattern, and treatment, and their association with induction chemoradiotherapy and influence on survival.

Methods: Between March 1987 and November 2001, 291 patients with clinical stage ≥IIA esophageal cancer underwent esophagectomy; 106 received induction chemoradiotherapy. A propensity score incorporating clinical stage and histopathology was used to identify 100 matched pairs of induction chemoradiotherapy and surgery-only patients. Among these, occurrence of pleural effusion, pericardial effusion, and pericarditis was ascertained by follow-up. Time-related occurrence, risk factors, and association with survival were assessed by repeated-events analyses.

Results: During follow-up, 61 induction chemoradiotherapy patients experienced at least one pleural or pericardial complication, as did 46 propensity-matched surgery-only patients. Most occurred within 1 year, with 1-year freedom from occurrence only 34% after induction chemoradiotherapy and 59% after surgery only ($p = 0.02$). Risk of pleural effusion was nearly twice as great (hazard ratio 1.7, $p = 0.0004$) and pericardial complications 5 times greater (hazard ratio 5.3, $p = 0.0005$) after induction chemoradiotherapy than after surgery alone. Complications after induction chemoradiotherapy required intervention somewhat more frequently (58% versus 47%, $p = 0.18$), although they did not diminish subsequent survival ($p > 0.8$).

Conclusions: Benign pleural and pericardial complications occur surprisingly frequently after esophagectomy, particularly when induction chemoradiotherapy is employed. This must be factored into discussions of morbidity for multimodality treatment strategies for locally advanced esophageal cancer and should be considered distinct from acute toxicity of induction chemoradiotherapy reported.

Key Words: Pleural effusion, Pericardial effusion, Pericarditis, Multimodality therapy.

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Although safety of esophageal resection for carcinoma has steadily improved,[1] it remains one of the most morbid elective operations. Adding to the procedure's magnitude has been the use of induction chemoradiotherapy for locally advanced cancer,[2–4] which has affected both short- and long-term outcomes.[5,6]

An unexpected clinical observation was that patients treated with induction chemoradiotherapy frequently presented after esophagectomy with *benign* pleural and pericardial complications. Consequently, we designed a study to (1) document occurrence, temporal pattern, and treatment of these complications in comparable patients, (2) test the hypothesis that they occurred more frequently in patients receiving induction chemoradiotherapy, and (3) assess their influence on survival.

PATIENTS AND METHODS

Patients

Between March 1987 and November 2001, 291 patients with clinical stage IIA or greater carcinoma of the esophagus underwent esophagectomy via thoracotomy at Cleveland Clinic.[7] Of these, 106 (36%) received induction chemoradiotherapy. Patient and tumor characteristics and operative details were extracted from the Esophagectomy Database, which has been approved for use in research by the Institutional Review Board, with patient consent waived (Table 1). Patients selected for induction chemoradiotherapy were generally those with locally advanced cancers. This group of patients was deemed to have sufficient cardiopulmonary reserve to tolerate multimodality therapy.

Induction Chemoradiotherapy

Over the duration of the study, 3 main induction chemoradiotherapy regimens were used. The 2 most common

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TABLE 1. Patient and Tumor Characteristics and Their Therapy for All 291 Patients Undergoing Esophagectomy for Clinical Stage IIA or Greater Carcinoma of the Esophagus

Characteristic	Induction Chemoradiotherapy (% of 106)	Surgery Only (% of 185)	*p*
Male	82	85	0.5
Age at esophagectomy (yr), mean ± SD	60 ± 9	62 ± 10	0.2
Caucasian	93	95	0.5
Clinical stage[a]			0.002
IIA	34	54	
IIB	6	4	
III	58	42	
IVa	3	0	
Histopathologic type			
Adenocarcinoma	74	83	0.05
Histologic grade			0.04
Well differentiated	9	6	
Moderately differentiated	25	39	
Poorly differentiated	65	55	
Induction regimen			
Radiotherapy + 5-FU/cisplatin	71	—	
Radiotherapy + paclitaxel/ cisplatin	29	—	
Total radiation dose (Gy), mean ± SD	4200 ± 580	—	
Postoperative chemoradiotherapy	42	35	0.2

[a] Greene FL, Page DL, Fleming ID, Fritz AG, et al. (Eds.), American Joint Committee on Cancer Staging Manual, 6th Ed. New York: Springer, 2002, Pp. 91–98.
SD, standard deviation; 5-FU, fluorouracil.

were (1) 2 cycles of cisplatin (20 mg/m^2/d) and 5-fluorouracil (1000 mg/m^2/d), both given as continuous intravenous infusions for 4 days, with concomitant hyperfractionated radiation (150 cGy bid) to the mediastinum to a total dose of 4500 cGy, all administered 1 month before surgery[8]; and (2) the same protocol with a 24-hour intravenous infusion of paclitaxel (175 mg/m^2) in place of 5-fluorouracil.[9] A lesser used regimen consisted of 1 cycle of cisplatin and 5-fluorouracil along with hyperfractionated radiation of 3000 cGy.[10] Patients tolerating this therapy and without evidence of disease progression proceeded to esophagectomy, usually within 6 weeks of completion of chemoradiotherapy.[10] We attempted to adjust for small variations in doses and dosing schedules in our multivariable analyses.

Some patients received postoperative chemoradiotherapy, similar to the preoperative regimen, with adjustments for amount of preoperative radiation.[8–11] Acute toxicities of these chemoradiotherapy regimens have been reviewed elsewhere.[8–10]

Benign Pleuropericardial Complications

By medical record examination and systematic structured interview of patients and their families, all pleural and pericardial complications (*benign or malignant*), their date of occurrence, and management were identified—pleural effusion, chylothorax, empyema, pericardial effusion, and pericarditis. This study focuses on *benign* pleural and pericardial effusions and pericarditis, defined as follows:

- Benign pleural effusion: Pleural fluid identified on routine or symptom-directed chest radiogram, deemed by attending surgeon or oncologist to be new or to represent a substantial increase from initial postoperative studies, and for which investigation revealed no evidence of malignancy, hemothorax, chylothorax, or empyema. Effusions without cytology were considered benign if follow-up radiograms demonstrated either no change or resolution, and there was no evidence of cancer recurrence elsewhere.
- Benign pericardial effusion: Accumulation of pericardial fluid identified on routine or symptom-directed chest computed tomography or echocardiography and for which investigation revealed no evidence of malignancy or infection. Effusions without cytology were considered benign if follow-up studies demonstrated either no change or resolution, and there was no evidence of cancer recurrence elsewhere.
- Benign pericarditis: Inflammation of the pericardium diagnosed by a combination of physical examination, electrocardiogram, chest computed tomography, and echocardiography, for which investigation revealed no evidence of malignancy.

Analytic Approach

To meaningfully understand these complex data and develop valid inferences, the following had to be considered.

1. Induction chemoradiotherapy was not administered to patients in a randomized fashion. Therefore, we had to simulate a randomized trial by established statistical methods to generate well-matched study groups.[12–14]
2. Pleural and pericardial complications occurred over a time span of several months. Therefore, well-established time-related methods were used.[15–17]
3. These complications were not always singular or mutually exclusive. Therefore, patients continued to be tracked after occurrence of a complication using repeated events analyses.[15,17]
4. Patients could die of their underlying cancer before a pleural or pericardial complication. Therefore, death served as a competing risk with occurrence of these complications, for which competing risk analysis was required.[18]
5. The complications could importantly impact patient survival; therefore, we estimated the possible increased death rate attributable to each complication occurrence.[19,20]

Methodologic Details

Study Design

Induction chemoradiotherapy was not administered to patients with esophageal cancer in a randomized fashion. Therefore, consistent with Rubin's strategy of study design versus outcome analysis,[14] we designed an "approximate randomized study" to test our hypothesis. Nonparsimonious logistic regression analysis was used to estimate the propen-

sity of each patient to receive induction chemoradiotherapy based on pretreatment clinical stage, histopathologic type, and histopathologic grade (G), without regard for outcome. Separate analyses were performed for patients who did (C = 0.65) and did not (C = 0.68) receive postoperative chemoradiotherapy. From the resulting logistic regression equations, the probability of receiving induction chemoradiotherapy was calculated for each patient (propensity score).[12,13] This propensity score was used as the sole variable to match patients who did versus did not receive induction chemoradiotherapy. Greedy matching was employed,[21] resulting in matching 41 of 45 patients receiving both pre- and postoperative chemoradiotherapy and 59 of 61 who received only induction chemoradiotherapy, a total (by chance) of 100 patients (94% of such patients), to 100 patients who underwent esophagectomy only without pre-or postoperative chemoradiotherapy (hereafter designated "surgery only"). Thus, the approximate randomized study for comparison of outcomes consisted of these matched groups. Characteristics of these 100 propensity-matched pairs are given in Table 2. To be conservative in our comparisons, nonpaired testing was performed, just as would be the case for a randomized trial.

Follow-Up

Although patients were routinely followed at least semiannually after esophagectomy, we conducted an additional cross-sectional follow-up of the matched patients that included review of clinical records, a mailed questionnaire, and telephone contact of patients or families failing to respond to the questionnaire. This review, the questionnaire, and telephone script were approved by Cleveland Clinic's Institutional Review Board, the latter two instruments with patient consent required. Follow-up was 100% complete, with mean follow-up of 8.3 ± 2.6 years among 34 patients alive at cross-sectional follow-up.

TABLE 2. Patient and Tumor Characteristics of Propensity-Matched Patients and Their Therapy

Characteristic	Induction Chemoradiotherapy (% of 100)	Surgery Only (% of 100)	*p*
Male	85	81	0.4
Age at esophagectomy (yr), mean ± SD	60 ± 9	61 ± 11	0.4
Caucasian	93	96	0.4
Clinical stage[a]			0.6
IIA	34	35	
IIB	6	6	
III	58	59	
IVa	2	0	
Histopathologic type			
Adenocarcinoma	74	77	0.6
Histologic grade			0.3
Well	10	5	
Moderate	27	29	
Poor	63	66	
Induction regimen			
Radiotherapy + 5-FU/cisplatin	73	—	
Radiotherapy + paclitaxel/cisplatin	27	—	
Total radiation dose (Gy), mean ± SD	4200 ± 590	—	
Postoperative chemoradiotherapy	41	41	1.0

[a] Greene FL, Page DL, Fleming ID, Fritz AG, et al. (Eds.), American Joint Committee on Cancer Staging Manual, 6th Ed. New York: Springer, 2002, Pp. 91–98.
SD, standard deviation; 5-FU, fluorouracil.

Complication Occurrence and Temporal Pattern

Benign pleural and pericardial complications did not occur within a narrow postoperative time span, but were distributed over several months. Further, they often recurred. Thus, simple proportions of patients experiencing versus not experiencing these complications did not accurately reflect the outcome, nor could simple "terminating event" actuarial methods be employed, because they do not account for recurrence of an event. Thus, each benign pleural or pleuropericardial complication was analyzed as (1) time to first occurrence and (2) a time-related repeated event. A repeat complication was defined as recurrence beyond 30 days of a previous complication of that type, independent of treatment.

Kaplan-Meier analysis was used to estimate freedom from first event,[16] and Nelson's cumulative event analysis was used for nonparametric estimation of cumulative incidence, expressed as number of complications per patient.[17] Multiphase hazard function methodology was used to characterize temporal pattern of occurrence.[15] (For additional details, see http://www.clevelandclinic.org/heartcenter/hazard.) The primary motivation for use of a multiphase hazard model was that visual inspection of nonparametric estimates (Kaplan-Meier and Nelson) revealed a temporal pattern indicating important change in risk across time. Generally, this implies nonproportional hazards with different risk factors modulating early and later time periods. The methodology selected addresses these kinds of data. Using these techniques, freedom from, cumulative incidence of, and hazard for complications were estimated for benign (a) pleural effusion, (b) pericardial effusion, (c) pericarditis, and (d) the combination of these.

Influence of Induction Chemoradiotherapy on Complications

Although patients were propensity matched—rendering comparisons of outcomes risk adjusted—we nevertheless performed multivariable parametric analysis of the events to be sure that another variable confounded with use of induction chemoradiotherapy did not emerge. For this, the variables in the Appendix, and the indicator for whether or not induction chemoradiotherapy had been used, were tested. These variables included preoperative, postoperative, and cumulative cycles of chemotherapy and dose of radiation.

Influence of Complications on Subsequent Survival

To assess the possible influence of these complications on subsequent survival, we employed modulated-renewal-process methodology (this industrial technique gave rise to

expressions such as "good as new").[19,20] For it, time zero was reset at each complication. Thus, patients experiencing a first event were censored at time of occurrence, restarted at a new time zero, and traced to occurrence of a second event, and so forth, for each successive event.[19]

A novel aspect of the present study is that we then investigated survival within this modulated-renewal context, treating death as a competing risk. This permitted us to investigate the possible influence on survival of not only patient and tumor characteristics and use of induction chemoradiotherapy, but also of timing and number of postesophagectomy complications. Nonproportionality of risk was again accommodated by multiphase hazard methodology.[15]

Presentation

Categorical variables are summarized as frequencies and percentages and compared by χ^2 testing or Fisher's exact test. Continuous variables are summarized as mean ± SD and compared by *t* test, or summarized as median and interquartile range and compared by Wilcoxon rank sum test. Time-related event estimates are presented with 68% asymmetric confidence limits (CL) equivalent to ±1 standard error.

RESULTS

Complication Occurrence, Timing, and Influence of Induction Chemoradiotherapy

During follow-up after esophagectomy, 61 of the 100 propensity-matched induction chemoradiotherapy patients experienced 118 benign pleural and pericardial complications, and 46 propensity-matched surgery-only patients experienced 72 (Table 3). One-year freedom from occurrence of the first of these complications was only 34% among induction chemoradiotherapy patients compared with 59% of surgery-only patients ($p = 0.02$, Figure 1). Most complications occurred within the first postoperative year, although early risk (hazard) was more protracted in the induction chemoradiotherapy group (Figure 2*A*). By 1 year, the number of complications was 1.3 events per patient in the induction chemoradiotherapy group, more than twice that after surgery alone (0.61 events per patient; $p = 0.02$, Figure 2*B*).

Influence of Induction Chemoradiotherapy on Individual Complications

The most commonly occurring complication was pleural effusion (Figure 3), and risk of its occurrence was nearly twice as great after induction chemoradiotherapy than after surgery only (hazard ratio, 1.7; CL: 1.5–2.0; $p = 0.0004$). Risk of a pericardial complication (effusion or, less commonly, pericarditis) was more than 5 times as great after induction chemoradiotherapy (Figure 4; hazard ratio, 5.3; CL: 3.3–8.6; $p = 0.0005$).

Treatment of Complications

Of 118 complications occurring in induction chemoradiotherapy patients, 68 (58%) required specific therapeutic interventions, as did 34 of 72 (47%) in surgery-only patients ($p = 0.18$; Table 4). Eighteen therapeutic interventions were required in induction chemoradiotherapy patients for 32 benign pericardial complications (56%), as were 3 interventions for 11 complications (27%) among surgery-only patients ($p = 0.16$). Overall, 33 induction chemoradiotherapy patients underwent therapeutic interventions for pleural and pericardial complications, compared with 24 surgery-only patients ($p = 0.2$).

TABLE 3. Number of Benign Pleural or Pericardial Complications per Patient

Complication	Induction Chemoradiotherapy (% of 100)	Surgery Only (% of 100)
Pleural effusion		
0	44	54
1	38	34
2	12	10
3 or more	6	2
No. of complications	86[a]	61[a]
Pericardial effusion		
0	79	91
1 or more	21	9
No. of complications	25[a]	9[a]
Pericarditis		
0	94	98
1 or more	6	2
No. of complications	7[a]	2[a]
Any pleural or pericardial complication		
0	39	54
1	36	28
2	9	12
3	8	5
4 or more	8	1
Total complications	118	72

[a] Total number of each type of complication experienced during follow-up.

Influence of Complications on Subsequent Survival

Although early survival appeared to be somewhat worse after a pleural or pericardial complication than before any such occurrence (Figure 5), nonproportional hazards evaluation (which can account for "crossing lines" of risk) indicates that the hazard function for death after each occurrence was similar ($p = 0.5$). This meant that patients returned each time to the somewhat higher early post-treatment risk of death. Although the cumulative effect of these recurring risks for mortality might adversely affect survival, for patients receiving induction chemoradiotherapy, survival was similar whether or not complications occurred (p [log-rank] = 0.5); the same was true of patients who did not receive induction chemoradiotherapy (p [log-rank] = 0.2). Severity of complications, expressed as requirement for surgical intervention, did not affect survival, whether or not induction chemoradiotherapy was used (p [early hazard phase] >0.9, p [late hazard phase] = 0.5).

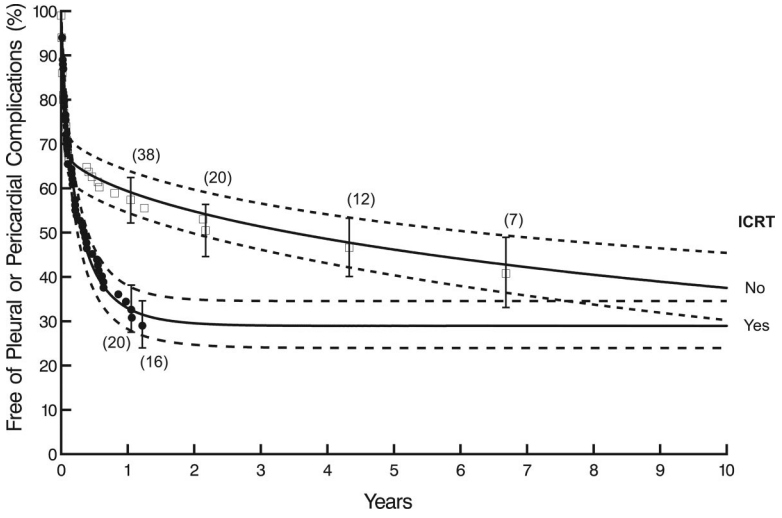

FIGURE 1. Freedom from benign pleural or pericardial complications after esophagectomy according to whether or not induction chemoradiotherapy (ICRT) had been administered (propensity-matched patients). Symbols represent first-occurring complication, vertical bars 68% confidence limits (CL) equivalent to ±1 standard error, and numbers in parentheses patients remaining at risk (Kaplan-Meier product limit estimates[16]). Solid lines enclosed within dashed CLs represent parametric estimates.[15]

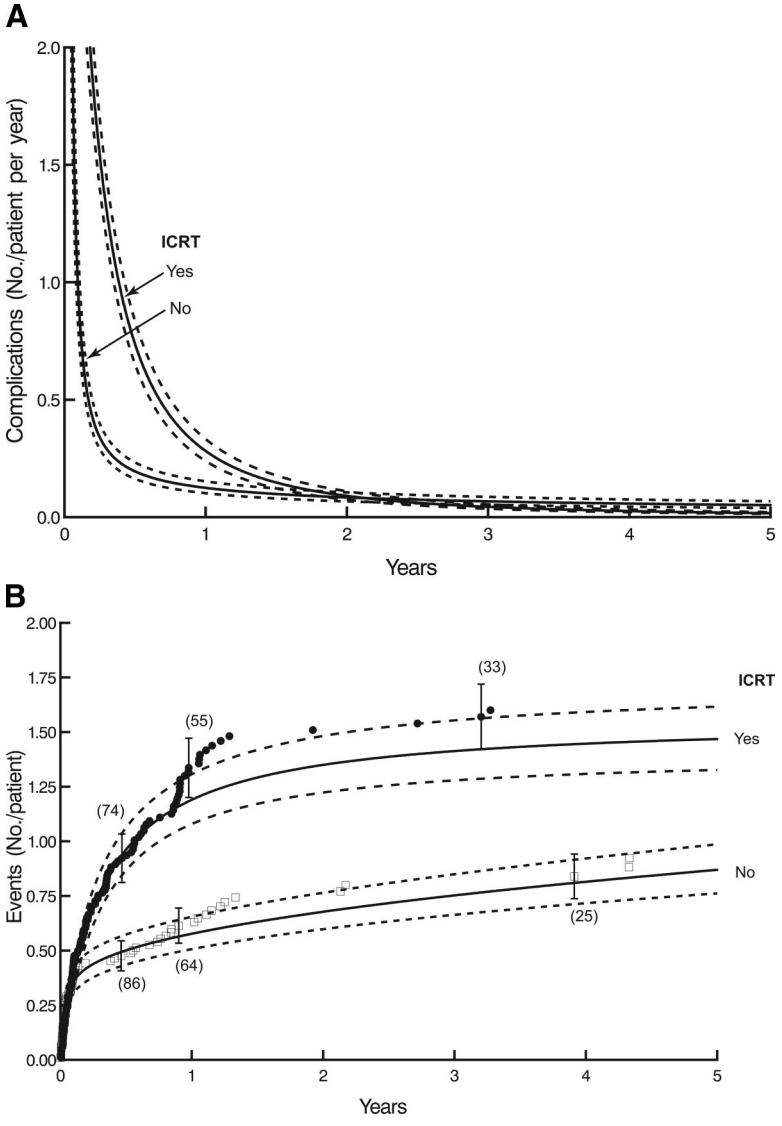

FIGURE 2. Benign pleural or pericardial complications after esophagectomy, according to whether or not induction chemoradiotherapy (ICRT) had been administered (propensity-matched patients). Analysis includes all ICRT events. *A,* Incidence (hazard function[15]). Dashed lines represent 68% confidence limits (CL). *B,* Cumulative incidence. Symbols represent individual events, vertical bars nonparametric 68% confidence limits, and numbers in parentheses patients remaining at risk (Nelson cumulative hazard repeating event method[17]). Solid lines are parametric estimates enclosed within dashed 68% CLs.[15]

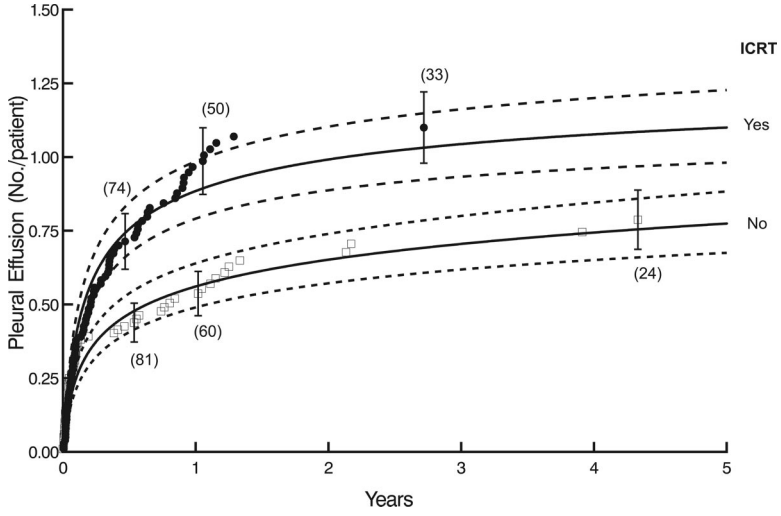

FIGURE 3. Cumulative incidence of benign pleural effusion after esophagectomy, according to whether or not induction chemoradiotherapy (ICRT) had been administered (propensity-matched patients). Format is as in Figure 2*B*.

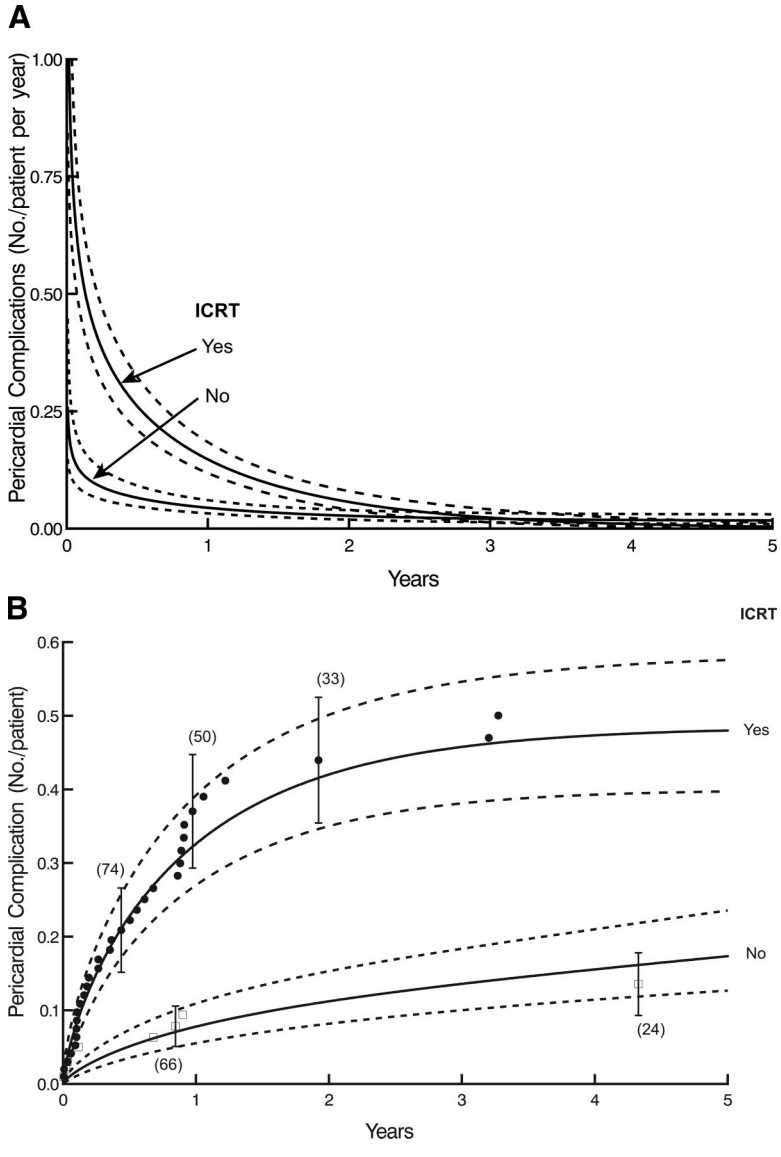

FIGURE 4. Benign pericardial complications (pericardial effusion or pericarditis) after esophagectomy, according to whether or not induction chemoradiotherapy (ICRT) had been administered (propensity-matched patients). Format is as in Figure 2. *A,* Incidence. *B,* Cumulative incidence.

TABLE 4. Interventions for Benign Pleural and Pericardial Complications

	Complications							
	Pleural Effusion		Pericardial Effusion		Pericarditis		Any Complication	
Intervention	**ICRT**	**Surgery Only**	**ICRT**	**Surgery Only**	**ICRT**	**Surgery Only**	**ICRT**	**Surgery Only**
Intervention performed[a]	50 (58)	31 (51)	12 (48)	2 (22)	6 (86)	1 (50)	68 (58)	34 (47)
Intervention type[b]								
Medical	45 (90)	24 (77)	7 (58)	1 (50)	4 (67)	0 (0)	56 (82)	25 (74)
Surgical	1 (2)	0 (0)	5 (42)	1 (50)	2 (33)	1 (100)	8 (12)	2 (6)
Medical and surgical	4 (8)	7 (23)	0 (0)	0 (0)	0 (0)	0 (0)	4 (6)	7 (21)
Total complications	86	61	25	9	7	2	118	72

[a] Number and, in parentheses, percent of complications.
[b] Number and, in parentheses, percent of interventions.
ICRT, induction chemoradiotherapy.

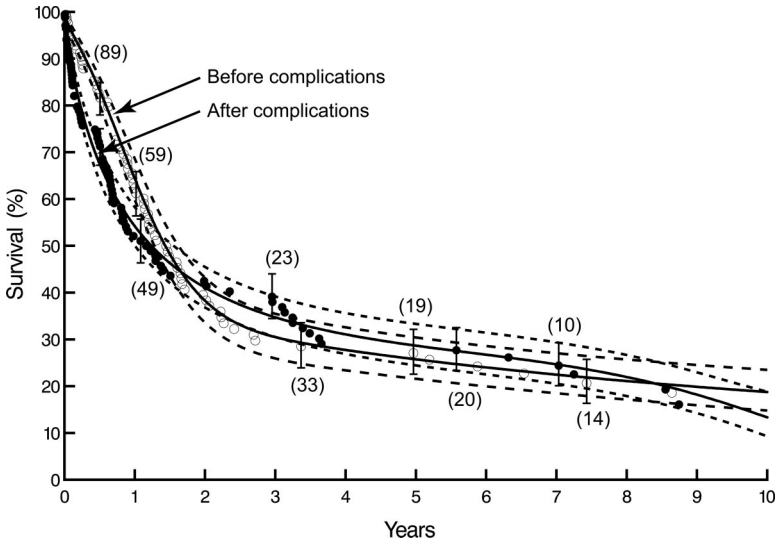

FIGURE 5. Survival following esophagectomy, before and after occurrence of pleuropericardial complications. Format is as in Figure 2. Open circles represent survival before the competing risk of a pleuropericardial complication and closed circles survival after a complication.

DISCUSSION

Principal Findings

Complication Occurrence and Timing

Locally advanced esophageal cancer portends an ominous prognosis. Because of this, attempts to combine therapies, both in the induction (preoperative) and consolidation (postoperative) settings, have experienced a renaissance. To date, however, the efficacy of multimodality treatments, incorporating surgical resection as their thrust, have yielded fairly disappointing results, with, at best, minimal improvement in survival.[2,6]

Regardless of impact on survival, it has often been reported that induction chemoradiotherapy for locally advanced esophageal cancer is well tolerated and is not accompanied by additional perioperative morbidity.[5,22] Although these conclusions seemed difficult to accept, it is easy to conceive that a small additional morbidity caused by induction chemoradiotherapy could be statistically unrecognized in the setting of esophagectomy only—an enormously morbid procedure by itself. What has been overlooked are late manifestations of induction chemoradiotherapy. We were therefore surprised to find what appeared to be an extraordinary number of benign pleural and pericardial complications contributing to late morbidity in our series of patients with advanced-stage esophageal cancers.

Assessing these complications is not a simple task, however. They are time related, but analysis must account for the competing risk of death and mandates vigilant follow-up. Nonetheless, we have undertaken this task and can now demonstrate that induction chemoradiotherapy does indeed increase morbidity, specifically, postesophagectomy benign pleural and pericardial complications, which often required intervention to control, but appeared to have little demonstrable impact on patient survival.

Influence of Induction Chemoradiotherapy on Complications

This study was not designed to determine a clinical benefit from our induction chemoradiotherapy regimen; that has been reported earlier.[8–10] Rather, our intent was to discover a reason for the increasing pleural and pericardial complications observed after esophagectomy. Induction chemoradiotherapy impressively increased early risk of these benign pleural and pericardial complications, translating into nearly a twofold higher incidence within the first year. The

greatest risk was for pericardial complications, with a more than fivefold incidence above that observed with esophagectomy only.

We suspect that additional toxicity of induction chemoradiotherapy is attributable primarily to mediastinal radiation, with perhaps a sensitizing effect of chemotherapy, although we cannot discount a possible contribution from malnutrition or protein-losing enteropathy. The effects of ionizing radiation on mediastinal structures are complex. Radiation-induced heart disease, pneumonitis, and pleuritis have been documented in both acute and chronic settings [23–26]. These complications occur frequently when chemoradiotherapy is used as primary therapy for mediastinal cancer. In fact, echocardiographic evidence of pericardial disease can be observed in 40% of patients followed at least 5 years after mediastinal lymphoma treatment.[27]

There is little doubt that esophagectomy itself, without chemoradiotherapy, is a risk factor for these complications, although this could not be evaluated against chemoradiotherapy alone. Patients in the series had locally advanced adenocarcinoma of the esophagus and, regardless of whether induction chemoradiotherapy was given, underwent esophagectomy with *en bloc* abdominal and posterior mediastinal (two-field) lymphadenectomy.[7] Moreover, the thoracic duct was often resected, although the posterior pericardium was always left intact. Disruption of lymphatic channels investing the region was likely complete, and consequently, it is not surprising that pleural or pericardial effusion complicated the postoperative course to some degree even in the absence of induction chemoradiotherapy.

Treatment

Particularly troubling is that these pleural and pericardial complications following esophagectomy for cancer are not simply nuisances that abate spontaneously; they often persist and require intervention. This seems particularly true when induction chemoradiotherapy is given, although the data are inconclusive on this point. A brief, early report documented 15% reintervention for general pleural and pericardial complications among patients surviving at least 5 months after induction chemoradiotherapy and esophagectomy for squamous cell cancer.[28]

Although most of the interventions were uncomplicated aspirations, delay in diagnosing slowly worsening pleural effusion may have led to more complex operative interventions in some patients. Because of this, after early postesophagectomy recovery, patients who receive induction chemoradiotherapy are now routinely seen at 3-month intervals, with chest imaging for 2 years and then every 6 months up to 5 years. In the absence of specific heart imaging, any concerning auscultatory finding (e.g., rub, muffled tones) mandates echocardiography. It has more recently become our practice that patients who redevelop pleural effusion after thoracentesis proceed to thoracoscopy and pleurodesis in an attempt to prevent entrapped lung syndrome.

Surprisingly, depending on the degree of pleuritis and pleural fibrosis induced by radiation, chemical pleurodesis is often ineffective in palliating recurrent benign pleural effusion after induction chemoradiotherapy. The avascular, densely fibrotic parietal pleura over the lower hemithorax does not provide a good substrate for pleural symphysis. In these cases, it may be prudent to add a local pleurectomy, because this exposes the healthier, better vascularized endothoracic fascial layer as the adherent surface. It is conceivable that these patients can be recognized by preoperative imaging studies.

Influence of Complications on Subsequent Survival

Occurrence of each complication seems to expose the patient to a transient period of high risk that quickly subsides and returns to a precomplication level. Among the patients in this study, the number of occurrences and recurrences has been insufficient to suggest a survival impact. However, it is conceivable that a small deleterious effect on survival may be hidden, given the overwhelming risk of death from cancer recurrence in these patients.

Limitations

We interpreted pleural and pericardial complications as benign when cytology was available and they resolved, or were not followed by cancer recurrence elsewhere. This may overestimate occurrence of these complications, because some could have been malignant (false positives), which would, in turn, underestimate cancer recurrence.

It is comforting to note that there was little survival difference between patients with and without pleural and pericardial complications, which supports our contention that these are benign occurrences.

An important limitation is that patients were not randomly assigned to receive induction chemoradiotherapy. Decision to use induction chemoradiotherapy was not protocolized, at times it was not available, and occasionally patients declined it. This resulted in considerable heterogeneity in cancer stage among patients undergoing surgery alone and those receiving induction chemoradiotherapy. This overlap of patient and cancer characteristics allowed us to use an approximate randomized study design to explore whether induction chemoradiotherapy increased risk of these complications. All but 6 patients receiving chemoradiotherapy could be matched. Further, patients tolerate induction chemoradiotherapy differently with regard to threshold of toxicity development. This clearly affects the absolute amount of induction treatment that can be delivered to a specific patient and, consequently, creates heterogeneity in the treatment group. This problem cannot easily be accounted for in an analysis of this limited size, despite including total dose of radiation and number of chemotherapy cycles completed as variables.

This was a single-institution study, which permitted in-depth review of these complications, but may limit generalizability. We are also uncertain of the generalizability of these findings because induction chemoradiotherapy regimens among institutions vary.

CONCLUSIONS

Perioperative and immediate postoperative complications of esophageal resection performed after induction chemoradiotherapy have been chronicled elsewhere.[9,29] Particu-

larly concerning are problems arising well after apparent recovery that continue to contribute to morbidity and that may ultimately reduce efficacy of multimodality treatment regimens. Of importance, these are seldom documented or captured during the short follow-up afforded most patients because of the competing risk of death from cancer recurrence that tends to confound the latent appearance of benign complications.

When documented early, aggressive management may avoid subsequent extensive operative interventions. These insidious complications must be discussed with patients as possible risks when considering enrollment in induction chemoradiotherapy protocols for locally advanced esophageal cancer and are distinctly different from the acute toxicities of multimodality therapy that are standardly reported.

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APPENDIX: VARIABLES EXAMINED IN MULTIVARIABLE ANALYSES

Demography: Age, sex

Preoperative therapy: Paclitaxel + cisplatin (cycles), 5-fluorouracil + cisplatin (cycles), radiation dose (Gy), any chemoradiotherapy

Tumor characteristics: Adenocarcinoma, squamous cell carcinoma, histologic grade (G) (well differentiated, moderately differentiated, poorly differentiated/undifferentiated)

Clinical stage: IIA, IIB, III/IVa

Pathologic stage: All stages, down-staged (yes/no)

Postoperative therapy: Paclitaxel + cisplatin (cycles), 5-fluorouracil + cisplatin (cycles), radiation dose (Gy), any chemoradiotherapy

Procedure: Date of esophagectomy

